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PROSTAGLANDIN E₂ PROMOTES RECOVERY OF HEMATOPOIETIC STEM AND
PROGENITOR CELLS AFTER RADIATION EXPOSURE

The hematopoietic system is highly proliferative, making hematopoietic stem and progenitor cells (HSPC) sensitive to radiation damage. Total body irradiation and chemotherapy, as well as the risk of radiation accident, create a need for countermeasures that promote recovery of hematopoiesis. Substantive damage to the bone marrow from radiation exposure results in the hematopoietic syndrome of the acute radiation syndrome (HS-ARS), which includes life-threatening neutropenia, lymphocytopenia, thrombocytopenia, and possible death due to infection and/or hemorrhage. Given adequate time to recover, expand, and appropriately differentiate, bone marrow HSPC may overcome HS-ARS and restore homeostasis of the hematopoietic system. Prostaglandin E₂ (PGE₂) is known to have pleiotropic effects on hematopoiesis, inhibiting apoptosis and promoting self-renewal of hematopoietic stem cells (HSC), while inhibiting hematopoietic progenitor cell (HPC) proliferation. We assessed the radiomitigation potential of modulating PGE₂ signaling in a mouse model of HS-ARS. Treatment with the PGE₂ analog 16,16 dimethyl PGE₂ (dmPGE₂) at 24 hours post-irradiation resulted in increased survival of irradiated mice compared to vehicle control, with greater recovery in HPC number and colony-forming potential measured at 30 days post-irradiation. In a sublethal mouse model of irradiation, dmPGE₂-treatment at 24 hours post-irradiation is associated with enhanced recovery of HSPC populations

compared to vehicle-treated mice. Furthermore, dmPGE₂-treatment may also act to promote recovery of the HSC niche through enhancement of osteoblast-supporting megakaryocyte (MK) migration to the endosteal surface of bone. A 2-fold increase in MKs within 40 μ m of the endosteum of cortical bone was seen at 48 hours post-irradiation in mice treated with dmPGE₂ compared to mice treated with vehicle control. Treatment with the non-steroidal anti-inflammatory drug (NSAID) meloxicam abrogated this effect, suggesting an important role for PGE₂ signaling in MK migration. *In vitro* assays support this data, showing that treatment with dmPGE₂ increases MK expression of the chemokine receptor CXCR4 and enhances migration to its ligand SDF-1, which is produced by osteoblasts. Our results demonstrate the ability of dmPGE₂ to act as an effective radiomitigative agent, promoting recovery of HSPC number and enhancing migration of MKs to the endosteum where they play a valuable role in niche restoration.

Louis M. Pelus, Ph.D., Chair

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